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STEVEN F. WEINSTOCK
ABBOTT LABORATORIES
100 ABBOTT PARK ROAD
DEPT. 377/AP6A
ABBOTT PARK, IL 60064-6008

EXAMINER	
CHUNDURU, SURYAPRABHA	
ART UNIT	**PAPER NUMBER**
1637	20

DATE MAILED: 06/01/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/747,538	KATZ ET AL.	
	Examiner	Art Unit	
	Suryaprabha Chunduru	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 February 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *17,18,38-41 and 43* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17,18,38-41 and 43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The decision on the petition under 37 CFR 1.137(b) filed on January 12, 2004, to revive the abandonment has been considered and the case is reopened for prosecution.

2. Applicants' response to the office action filed on January 12 has been entered.

3. Claims 17 and 38 are amended. New claim 43 is added. Thus claims 17-18, 38-41, 43 are pending.

4. The request for correction of inventorship is acknowledged. However the request was not accompanied by the statement required under 37 CFR 1.48(b)(2).

Response to Arguments

5. Applicants' response to the office action has been fully considered and found persuasive in part.

6. With reference to the rejection made in the previous office action under 35 USC 112, second paragraph, Applicants' arguments and amendment are fully considered and the rejection is with drawn in view of the amendment.

7. With reference to the rejection made in the previous office action under 35 USC 101, Applicants' arguments and amendment are fully considered and the rejection is withdrawn in view of the amendment.

8. The following is the rejection made in the previous office action under 35 USC 102(e):

A. Claims 17 and 18 are rejected under 35 U.S.C. 102(e) as being anticipated by Wittwer et al. (USPN. 6,232,079).

Wittwer et al. teach a method for detecting a target nucleic acid sequence in a test sample comprising (a) contacting the test sample with amplification reagents comprising a polymerase, a

PCR primer pair, and a probe (see column 6, lines 1-15, column 44, lines 24-38); (b) performing PCR cycles (i) raising temperature to dissociate the double-stranded genomic DNA, lowering the temperature to allow primers and probe to hybridize to the target nucleic acid, raising the temperature to dissociate the target-probe hybrids and extending the primers and continuously raising the temperature to temperature dependent polymerase extension (see column 44, lines 50-67, column 45, lines 1-12); (c) repeatedly performing the PCR cycles to form an amplification product (see column 45, lines 13-53) and (d) detection of the amplification product as an indication of presence of the nucleic acid (see column 45, lines 13-53). Wittwer et al. also disclose that the target nucleic acid sequence is a polymeric nucleic acid sequence (see column 44, lines 24-38). Thus the disclosure of Wittwer et al. meets the limitations in the instant claims.

Response to arguments:

Applicants' arguments and amendment are fully considered and found not persuasive. Applicants argue that Wittwer teaches continuous temperature rather than discrete or discontinuous change in temperature and the amendment clearly recites discontinuous change in temperature, which recites four-step PCR process. Accordingly Wittwer does not teach or suggest discontinuous temperature four-step PCR process. Applicants' arguments are fully considered and found not persuasive. Wittwer et al. teach discontinuous change in temperature as claimed in claim 17, that is on column 44, lines 53-58, Wittwer et al. teach maintaining the reaction at a temperature (94^0 C) to dissociation or denaturation of double-stranded nucleic acid sequences (step b-i); maintaining the reaction at a temperature (50^0 C) sufficient to anneal the primers to the target nucleic acid (step b-ii); maintaining the reaction for a time at temperature (72^0 C) sufficient to extend the primers (step b-iii); raising the temperature of the reaction to a temperature (94^0 C) to

monitor the primer extension product. Thus Wittwer et al. teach discontinuous change in temperature and the four-step PCR process and the rejection is maintained herein.

9. The following is the rejection made in the previous office action under 35 USC 102(e):

B. Claims 17-18, 38-41 are rejected under 35 U.S.C. 102(e) as being anticipated by Lapidus et al. (USPN.6,143,529).

With reference to the instant claims 17 and 18, Lapidus et al teach a method for detecting a target nucleic acid sequence comprising (a) contacting a test sample with a probe, a pair of primers and amplification reagents (see column 10, lines 29-67); (b-c) performing repeated PCR cycles comprising raising temperature (denaturation cycle), annealing cycle, primer extension cycle followed by one cycle of primer extension (see column 11, lines 37-40); (d) detecting the amplification product as an indication of the presence of the nucleic acid in the test sample (see column 11, lines 64-67, column 12, lines 38-43). Lapidus also disclosed that the method comprises target nucleic acid comprising a ploymorphic nucleic acid sequence (see column 13, lines 8-52).

With reference to the instant claims 38-40, Lapidus et al. teach a method for detecting a deletion or insertion in a target nucleic acid suspected to have greater than 200bp long or less than 200bp long (see column lines 36-51) wherein the method comprises (a and b) contacting a patient sample (test sample) comprising a known standard sequence and a sequence having suspected mutation with amplification reagents to form a reaction mixture and subjecting the reaction mixture to amplification conditions (see column 8, lines 54-67, column 9, lines 1-67, column 10, lines 1-67, column 11, lines 37-67, column 12, lines 38-43); (c) detecting a first signal proportional to the amount of target nucleic acid (see column 13, lines 55-67, column 14,

lines 1-49); (d) detecting a second signal that is proportional to the amount of the standard nucleic acid amplification product (column 12, lines 38-67, column 13, lines 1-14); (e) comparing the said amount of DNA in the sample with that of a standard nucleic acid and determining whether a deletion or insertion of greater or less than 200 bp is present in the test sample (see column 8, lines 4-13). Lapidus et al. discloses the mutation includes less than or greater than 200bp which includes the limitation in the instant claims 38-40.

With reference to the instant claim 41, Lapidus et al. disclose that the method comprises amplification conditions of the instant claim 17 (see column 10, lines 29-67, column 11, lines 37-67, column 12, lines 38-43). Thus the disclosure of Lapidus et al. meets the limitations in the instant claims.

Response to arguments:

With reference to the above rejection, Applicants' arguments and amendment are fully considered and are found not persuasive. Applicants argue that Lapidus et al. does not teach four-step PCR process and use of PCR primers that hybridize to target nucleic acid only if the target is present in a test sample and to a standard nucleic acid. Applicants' arguments are fully considered and found not persuasive. Lapidus et al. teach four-step PCR process on column 11, lines 37-40, where four discontinuous temperatures are used in the PCR process (94^0 C, 60^0 C, 72^0 C, and 72^0 C). Lapidus et al. also teach that the PCR reaction comprises target DNA:probe (DNA captured with probe), PCR primers (see column 10, lines 54-67). Further the claims are in open "comprising" format wherein any additional steps or elements could be included and meets the limitations as taught by Lapidus et al. Therefore the rejection is maintained herein.

10. With regard to the rejection made in the previous office action under 35 USC 103(a), Applicants' arguments and amendment to the claim 42 have been fully considered and the rejection is withdrawn herein in view of amendment and new grounds of rejection.

New Grounds of rejection necessitated by amendment

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 43 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lapidus et al. (USPN.6,143,529) and in view of Johansson et al. (Pharmacogenetics, Vol. 6, pp. 351-355, 1996).

Lapidus et al teach a method for detecting a target nucleic acid sequence comprising (a) contacting a test sample with a probe, a pair of primers and amplification reagents (see column 10, lines 29-67); (b-c) performing repeated PCR cycles comprising raising temperature (denaturation cycle), annealing cycle, primer extension cycle followed by one cycle of primer extension (see column 11, lines 37-40); (d) detecting the amplification product as an indication

of the presence of the nucleic acid in the test sample (see column 11, lines 64-67, column 12, lines 38-43). Lapidus also disclosed that the method comprises target nucleic acid comprising a ploymorphic nucleic acid sequence (see column 13, lines 8-52). Lapidus et al. also teach a method for detecting a deletion or insertion in a target nucleic acid suspected to have greater than 200bp long or less than 200bp long (see column lines 36-51) wherein the method comprises (a and b) contacting a patient sample (test sample) comprising a known standard sequence and a sequence having suspected mutation with amplification reagents to form a reaction mixture and subjecting the reaction mixture to amplification conditions (see column 8, lines 54-67, column 9, lines 1-67, column 10, lines 1-67, column 11, lines 37-67, column 12, lines 38-43); (c) detecting a first signal proportional to the amount of target nucleic acid (see column 13, lines 55-67, column 14, lines 1-49); (d) detecting a second signal that is proportional to the amount of the standard nucleic acid amplification product (column 12, lines 38-67, column 13, lines 1-14); (e) comparing the said amount of DNA in the sample with that of a standard nucleic acid and determining whether a deletion or insertion of greater or less than 200 bp is present in the test sample (see column 8, lines 4-13). Lapidus et al. discloses the mutation includes less than or greater than 200bp which includes the limitation in the instant claims 38-40. However, Lapidus et al. did not teach detection of gene deletions or insertions in CYP2D6 locus.

Johansson et al. teach a method for distinguishing the presence of a target nucleic acid and a variant which comprises a deletion (deletion of entire coding region (CYP2D6*5)), wherein Johansson et al. disclose that the method comprises contacting a test sample (containing DNA) with amplification reagents and a first and second amplification primer specific for the target site, subjecting the reaction mixture to amplification conditions, and detecting the

amplification product as an indication of the presence of the target nucleic acid sequence (see page 351, column 1, paragraph 1, and page 353, column 2, paragraph 1). Johansson et al. also teach that the method could be used to alter drug therapy (patient's care) and for evaluating the linkage between the CYP2D6 genotype and disease and aid in drug development (see page 354, column 2, paragraph 1).

Therefore, it would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made, to modify a for detecting a deletion or insertion in a target nucleic acid as a marker of a cancer or precancer as taught by Lapidus et al. with a method for detecting a variant (CYP2D6 gene deletion) as taught by Johansson et al. to achieve expected advantage of developing a method for enhanced sensitivity of detecting a target nucleic acid and its variant because Johansson et al. taught that CYP2D6 metabolizes more than 30 different drugs, and is highly polymorphic and was considered as important to develop simple PCR-based methods that could be used for efficient genotype analysis of ultrapid metabolizers which are involved in different drug design (see page 351, column 2, lines 15-18, abstract). An ordinary practitioner would have been motivated to combine the method of Lapidus et al. with the CYP2D6 marker as taught by Johansson et al. in order to achieve the expected advantage of developing a sensitive method for amplification because inclusion of highly polymorphic CYP2D6 marker would result in enhancing the sensitivity of the PCR method in characterizing complex polymorphic loci.

Conclusion

No claims are allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Suryaprabha Chunduru whose telephone number is 571-272-0783. The examiner can normally be reached on 8.30A.M. - 4.30P.M, Mon - Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and - for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Suryaprabha Chunduru
May 18, 2004

JEFFREY FREDMAN
PRIMARY EXAMINER